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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Andrew VAILLANT et al.
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Filing date:	September 12, 2003
For:	ANTIVIRAL OLIGONUCLEOTIDES TARGETING HBV
Art Unit:	1648
Examiner:	Bo, PENG
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DECLARATION UNDER 37 C.F.R. SEC. 1.132

I, Jean-Marc Juteau, do hereby declare and state as follows:

1. I received the degrees of Bachelor (B.Sc.) of Biology from Montreal University in 1985, Master (M.Sc.) of Microbiology and Immunology from Montreal University in 1988, and Doctor of Philosophy (Ph.D.) of Microbiology and Immunology from Laval University in 1991.
2. My academic background and experiences in the field of the present invention are listed on the enclosed *curriculum vitae.*
3. I am a founder and employee of REPLICor Inc. since 1999 and Senior Vice President since 2003.
4. I am an author of several scholarly publications as listed in my enclosed *curriculum vitae.*
5. I am an inventor in the present application; I have read and am thoroughly familiar with the contents of U.S. Patent Application Serial No. 10/661,088,

entitled "ANTIVIRAL OLIGONUCLEOTIDES TARGETING HBV", including the claims.

6. I have also read and understood the latest Official Action from the PTO dated January 24, 2007. In this Office Action, certain claims 3-32 were rejected for lack of enablement under 35 U.S.C. §112, first paragraph.

7. The following experiments had been performed in March-May 2007, under the supervision of Andrew Vaillant (inventor on this invention) and myself, to obtain results with a duck hepatitis B virus (duck HBV) model showing the anti-HBV activity of oligonucleotides of the present invention occurring by a non-sequence complementary mode of action, in a surrogate model of human HBV.

   The following experiment was conducted to evaluate the anti-viral activity of oligonucleotides occurring by a non-sequence complementary mode of action in ducks.

   Background of the model:

   References: Foster, WK *et al.* (2005) J. Virol. 79:5819-58-32; Funk A *et al.* (2007) World J. Gastroenterol. 13:91-103; Seignères B (2003) Antimicrob. Agents Chemother. 47:1842-1852 (copy of references enclosed with the present Declaration).

   To establish the suitability of an oligonucleotide (ON) as a therapy for HBV infection, we tested its ability to reduce serum viral titers in ducks infected with duck HBV.

Materials and Methods

Adolescent ducklings were infected with $5x10^8$ duck HBV virions (quantified in genomes by PCR) at day 0. Ducklings received placebo (normal saline) or 10mg/kg/day of REP 2006 (N_{40}), REP 2031 (C_{40}; corresponding to SEQ ID NO: 22 in USSN 10/661,088) or REP 2055 ($[AC]_{20}$; corresponding to SEQ ID NO: 24 in USSN 10/661,088) ONs formulated in normal saline. The animals were dosed daily using intraperitoneal injection administration for 4 days starting at day 0. Duck HBV infection and replication *in vivo* was monitored by assessment on duck HBVsAg immunoreactive cells in primary cultures taken from liver biopsies on day 4.

Results

The following table summarizes the ability of PS-ONs to inhibit duck HBV infection / replication *in vivo* in adolescent ducklings.

Table 1. Percentage of infected (duck HBVsAg positive) hepatocytes in duck HBV infected ducklings.

Day	Normal saline	REP 2006	REP 2031 (SEQ ID NO: 22)	REP 2055 (SEQ ID NO: 24)
4	2.728	0.006	0.429	0.0008

Furthermore, REP 2055 showed a strong response even at 14 days of administration (<0.0003% of infected hepatocytes). These results demonstrate that ONs of this invention display *in vivo* anti-HBV activity in the surrogate duck HBV model and are suitable for use in method of treatments of HBV infection in human patients.

8. The results presented above and produced according to the teaching of the present invention clearly proves that the present invention has clinical relevance and in

addition, that the *in vitro* results disclosed in the present application do not diverge from *in vivo* responses. The anti-HBV activity of the sequence oligonucleotides of the present invention occurring by a non-complementary mode of action is demonstrated in the DHBV model.

9. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by a fine or imprisonment, or both (18 U.S.C. Sec. 1001), and may jeopardize the validity of the application of any patent issuing thereon.

Signed  Dated: May 29, 2007

Jean-Marc Juteau